Remarks

Applicants have carefully considered this Application in connection with the Examiner's Action and respectfully request reconsideration of this Application in view of the following remarks.

I. Rejection under 35 U.S.C. §103(a)

The Examiner rejected Claims 1, 4, 5 and 6 under 35 U.S.C. §103(a) as being unpatentable over the Hcaplus Abstract 2001:167983 (WO 200101621, Cosford et. al.) and further in view of Blake et. al. and Patani et. al. Applicants respectfully traverse this rejection.

Applicants' claims define certain radiolabeled compounds useful as markers for neuroimaging (see Claim 4) and for labeling brain and peripheral nervous system structures involving mGlu5 receptors (see Claims 5 and 6), a process for the production of such compounds, compositions containing such compounds and a method for labeling brain and peripheral nervous system structures involving mGlu5 receptors using such compounds.

The Examiner states that the Hcaplus Abstract discloses a compound that differs from the instantly claimed compounds and compositions by "a substitution at the 2 position of the pyridyl ring, where by various forms of radiolabeled methyl (radiolabeled with stable isotopes) as stipulated in Claim 1 can be substituent in this position in the instant compound, whereas in the prior art compound, hydrogen is at the 2 position of the pyridyl ring." (See Office Action, the sentence bridging pages 2 - 3). The Examiner also states that Patani teaches that methyl is a bioisosteric replacement for hydrogen and that Blake teaches that stable isotopes are proving useful as tracers for drug distribution and metabolism studies. (See Office Action, page 3.) The Examiner then concludes that the claimed compounds are radiolabeled bioisosteres of the prior art compounds and that it would have been obvious for one of ordinary skill in the art to modify the prior art compounds to synthesize bioisosteres of the prior art compounds. (See Office Action, pages 3 and 4.)

As noted above, the Examiner states that the difference between Applicants' compounds and the prior art compound of the Hcaplus Abstract is "the teaching of a substitution at the 2 position of the pyridyl ring, where by the various forms of radiolabeled methyl ... can be the substituent in this position ... whereas in the prior art compound, hydrogen is at the 2 position of the pyridyl ring." (See Office Action, page 2.) Applicants would respectfully like to point out that the compounds of the present invention differ from this prior art compound in two respects:

1) the 2 position of the pyridyl ring in the prior art compound is hydrogen whereas the 2 position of the pyridyl ring in the present invention is non-radiolabeled methyl; and
2) the substituent on the cyclohexene ring is different in the present invention as compared to the prior art compound; the prior art compound has a non-radiolabeled O-methyl oxime substituent whereas the compound claimed in claim 1 of the present application has a radiolabeled O-C_1–C_4 alkyl oxime substituent.

In other words, the compounds of the present invention differ from the compound recited in the Hcaplus Abstract at two opposing ends of the molecule (one modification on the pyridyl ring and the other modification on the cyclohexene ring). In addition, the modification on the cyclohexene ring is not limited to a radiolabeled methyl group: the modification can include various radiolabeled C_2–C_4 alkyl groups.

The Examiner states that Patani et. al. at page 3152 teaches that methyl is a bioisosteric replacement for hydrogen. (See Office Action, page 3.) However, when Patani et. al. is closely examined, that conclusion is highly questionable. (It should be noted that Patani et. al. is a review article and not an article reporting laboratory research results of the authors or conclusions based on such laboratory research results.)

Patani et. al. sets forth several definitions of isosteres and bioisosteres, beginning with the definition of Langmuir. However, as set forth below, methyl does not appear to be an isostere or bioisostere of hydrogen under any of the definitions.

Langmuir Definition

Patani et.al. states that Langmuir compared the physical properties of various molecules and found them to be similar, and identified 21 groups of isosteres. It is disclosed in Patani et. al. on page 3148, the sentence spanning the left and right columns, that "isosteres were initially defined as those compounds or groups of atoms that have the same number and arrangement of electrons". As far as Applicants understand, H and CH_3 do not have "the same number and arrangement of electrons". It therefore follows that under Langmuir's definition, H and CH_3 do not appear to be isosteres.

Grimm's Hydride Displacement Law

It is disclosed in Patani et. al. on page 3148, right column, lines 13 – 22, that Grimm's Hydride Displacement Law states:

> Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively, to their right.

Thus, according to Grimm's Hydride Displacement Law, each vertical column of table 2 on page 3148 of Patani et.al. would represent a group of isosteres. Consequently, N and CH are isosteres; O, NH and CH_2 are isosteres; F, OH, NH_2 and CH_3 are isosteres; and Ne, FH, OH_2, NH_3 and CH_4 are isosteres. Therefore applying the principles of Grimm's Hydride Displacement Law to H, all that can be derived is that H_2 is an isostere of He.

Erlenmeyer Definition

According to Patani et. al. at page 3148, Erlenmeyer redefined isosteres as "atoms, ions and molecules in which the peripheral layers of electrons can be considered to be identical...." As far as Applicants understand, H and CH_3 do not have identical "peripheral layers of electrons". It follows that under Erlenmeyer's definition, H and CH_3 do not appear to be isosteres. If CH_3 were argued to be an isostere of H because its peripheral electrons are all hydrogen electrons, then any saturated

hydrocarbon – e.g., a C_{30} alkane – would be an isostere of H, a position which seems to Applicants to be wholly unsustainable.

Friedman Definition

As set forth in Patani et. al. on page 3148, right column, third through sixth lines after Table 3, "bioisosteres ... include all atoms and molecules which fit the broadest definition for isosteres and have a similar type of biological activity...." (emphasis added). As explained above, H and CH_3 do not appear to fit the Langmuir, Grimm's Hydride Displacement Law or Erlenmeyer definition of isosteres (i.e., do not appear to fit within the broadest definition for isosteres). Therefore, according to the Friedman definition of bioisosteres, H and CH_3 cannot be bioisosteres.

Burger Definition

On page 3 of the Office Action, the Examiner states that the definition of 'bioisosterism' has been broadened to mean "compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties". On page 3 of the Office Action, the Examiner is quoting the Burger definition of bioisosterism. (See Patani et. al., page 3148, right column, middle of the penultimate paragraph.) As far as Applicants understand, H and CH_3 do not have "near-equal molecular shapes and volumes" nor do they have "approximately the same distribution of electrons" at least in that, as Applicants understand, H has a single electron in a spherical 1s orbital (overlapping with its neighbouring C to form a C-H bond) whereas CH_3 has in addition to a 1s orbital, four $2sp^3$ hybrid orbitals of the carbon in a tetrahedral arrangement together forming C-H bonds with three hydrogens. Thus, contrary to what is stated by the Examiner, H and CH_3 do not appear to fall within Burger's definition of bioisosteres either.

Based on the foregoing, it is to be concluded that none of the definitions of isosteres or bioisosteres appearing on page 3148 of Patani et. al. would lead to the conclusion that hydrogen and methyl are isosteres or bioisosteres.

The Examiner contends that page 3152 of Patani et. al. teaches that methyl is a bioisosteric replacement for hydrogen. (See Office Action, page 3.) The heading in the

left-hand column after the first two paragraphs on page 3152 of Patani et. al. reads as follows: "4. Fluorine and Hydroxyl, Amino or Methyl Groups as Replacements for Hydrogen (Grimm's Hydride Displacement Law)".

However, there is nothing on page 3152 of Patani et. al. to support the statement contained in the heading. On page 3152 of Patani et. al., it can be seen that monovalent substitution by fluorine, hydroxyl and amino in place of hydrogen has been used in the design of metallopeptidase inhibitors (see Figure 11 and Table 9 on page 3152 of Patani et. al.). As can be seen, an increase in the effective van der Waal's radii resulted in a decrease in activity (i.e., R = H is more active than R = F, OH or NH_2). However, it should be pointed out that the replacement of hydrogen with methyl was not attempted.

Additionally, the effect of interchanging NH_2, OH and CF_3 was assessed. Table 10 and Figure 12 on page 3152 Patani et. al. show an increase in activity resulting from an increase in electronegativity (i.e., R = OH is more active than R = CF_3 or NH_2).

Nowhere on page 3152 of Patani et. al. is it disclosed that H can be substituted with CH_3. The only place in Patani et. al. where there is any alleged evidence that methyl is a bioisostere of hydrogen appears in Table 12 on page 3153 of Patani et. al. That table purports to show that Cl, CH_3, OH, NH_2 and H are bioisosteres. However, based upon the IC_{50} values set forth in Table 12, Cl is about 43 times more active than H and CH_3 is about six times more active than H. Such broad disparity in activity surely does not support the statement that Cl, CH_3, OH, NH_2 and H are bioisosteres with respect to the compound of Figure 14 on page 3153 of Patani et. al. Furthermore, looking at all of the examples on pages 3152 through 3155 of Patani et. al., it appears that whether or not something is concluded to be a bioisostere is rather subjective, unpredictable and context dependent.

Based upon the examples on pages 3152 through 3155 of Patani et. al., there is no experimental evidence that demonstrates that methyl is a bioisostere of hydrogen or that would give one of ordinary skill in the art any reasonable expectation that hydrogen and methyl have a similar type of biological activity. Furthermore, as noted above, under the various definitions of isosteres and bioisosteres in Patani et. al., it does not appear that methyl is a bioisostere of hydrogen. As a result, to conclude that methyl is

a bioisostere of hydrogen based upon the teachings of Patani et. al. is highly questionable, and the claimed compounds should not be characterized as radiolabeled bioisosteres of the prior art compounds.

Nevertheless, even if it were the case that it could be derived that methyl is a bioisostere of hydrogen, there are eleven different hydrogen atoms on the two rings of the prior art compound of the Hcaplus Abstract (four hydrogen atoms on the pyridyl ring and seven hydrogen atoms on the cylcohexene ring) that could be substituted by CH_3 and there are eight different carbon atoms (four on each ring) where the substitution could take place. There is nothing in the cited references that specifically teaches that one of the hydrogens on the prior art compound of the Hcaplus Abstract should be substituted with CH_3 much less that a hydrogen at the 2 position on the pyridyl ring should be substituted with CH_3. There must be some teaching or suggestion that would motivate one of ordinary skill in the art to make that substitution. In this case, there is no such teaching or suggestion.

Blake et. al. reviews laboratory studies involving deuterated drugs. In passing it mentions that "[s]table isotopes, particularly deuterium, are proving useful as tracers for drug distribution and metabolism studies." (See, Blake et. al., page 385.) The radioisotopes specifically mentioned in Blake et. al. are: deuterium, ^{13}C, ^{15}N, ^{18}O, ^{3}H and ^{14}C. Of these only ^{3}H is utilized in the present invention. However, it is taught at page 385 of Blake et. al. that ^{14}C and ^{3}H are disadvantageous when compared with deuterium and ^{13}C due to their larger mass difference. Thus, Blake et. al. specifically teaches away from using ^{3}H, and does not even mention ^{11}C, ^{123}I, ^{76}Br or ^{18}F. In other words, one or ordinary skill in the art reading Blake et. al. would not be motivated to use any of the isotopes that are used in the present invention. Furthermore, Blake et.al. does not provide any teaching or suggestion as to where the prior art compound of the Hcaplus Abstract should be radiolabeled.

As the Examiner will appreciate, the compound of Claim 1 where R is a methyl group has 15 carbon atoms, 16 hydrogen atoms, two nitrogen atoms and one oxygen atom that could be radiolabeled. This particular molecule could be radiolabeled with tritium at 16 potential positions and radiolabeled with ^{11}C at 15 different positions. Neither Blake nor any of the cited references provides any teaching or suggestion that

the radiolableling should take place only at R. In other words, there is no motivation for one of ordinary skill in the art to radiolabel the methyl group on the O-methyl oxime group on the prior art compound of the Hcaplus Abstract, much less to radiolabel it with ^{11}C or tritium. Furthermore, there is absolutely no teaching or suggestion that the methyl group on the O-methyl oxime group could be substituted with $(CH_2)_nX$ where n is 1, 2, 3 or 4 and X is ^{123}I, ^{76}Br or ^{18}F.

In order to achieve the present compounds, one of ordinary skill in the art must make two substitutions on the Hcaplus Abstract compound, namely a non-radiolabeled methyl substitution at the 2 position on the pyridyl ring and a radiolabeled C_1 to C_4 alkyl substitution on the oxime group on the cyclohexene ring wherein the isotope is either ^{11}C, ^{123}I, ^{76}Br or ^{18}F, which isotopes are not taught by any of the references, or is tritium, which Blake teaches is disadvantageous compared to deuterium. Given the multiple positions where the methyl substitution could be made for hydrogen, the multiple positions that could be radiolabeled, and the numerous number of isotopes that could be used, there are numerous radiolabeled compounds that could be generated by making substitutions on the prior art compound of the Hcaplus Abstract. Out of these numerous compounds, the applicants are only claiming 14 compounds plus their free base or acid addition salt forms.

One of ordinary skill in the art would not be motivated to generate these specific compounds based on the teachings of the cited references. Therefore, the claimed inventions are not obvious in view of the cited references. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Objection to Claim 3

Claim 3 was objected to by the Examiner for being based upon a rejected claim (i.e., Claim 1). In view of the arguments above with respect to the rejection of Claims 1, 4, 5 and 6 under 35 U.S.C. §103(a), Applicants believe that Claim 3 is allowable in its current form and does not need to be amended so that it is no longer dependent upon Claim 1.

III. Conclusion

In view of the foregoing, Claims 1, 3, 4, 5 and 6 are in condition for allowance, and Applicants earnestly solicit a Notice of Allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this Application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration to this Reply is respectfully requested.

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